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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/547,448 | 06/20/2006 | Ian Richard Matthews | 006090.00021 | 7662 |

22907 7590 02/05/2007

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| EXAMINER | |
|---|---|
| LEESER, ERICH A | |
| ART UNIT | PAPER NUMBER |
| 1624 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 02/05/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/547,448 | MATTHEWS, IAN RICHARD | |
| | Examiner | Art Unit | |
| | Erich A. Leeser | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) *25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/30/05*.

4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-29 are currently pending.

### *Priority*

Acknowledgment is made that this application is a U.S. national stage application of co-pending PCT application PCT/GB2004/001008 filed March 10, 2004, which was published in English under PCT Article 21(2) on September 23, 2004, and which claims the priority of Great Britain Patent Application No. 0305876.5, filed March 14, 2003 and Great Britain Patent Application No. 0319429.7, filed August 19, 2003.

### *Information Disclosure Statement*

The references filed on August 30, 2005, by Applicant are made of record.

### *Claim Rejections 35 U.S.C. § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 13, 26 and 27are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, an extra space is included before the "OH" of line 4 of claim 13. Correction of this obvious clerical error is requested.

Claim 26 is rejected because of the use of the term, "medicament." "Medicament" reads on the compound per se, so claim 26 might be viewed as a duplicate claim. Amendment to "pharmaceutical composition" and recitation of a pharmaceutically acceptable carrier, excipient or diluent, is recommended to comply with U.S. practice.

Claim 27 is rejected because it is unclear what is meant by the term "immunomodulation" as this term does not appear to be properly defined in the specification. Clarification is requested.

## *Claim Rejections – 35 U.S.C. § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 27-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, it is unclear what is meant by the term "immunomodulation" as this term does not appear to be properly defined in the specification. The common definition of the

term would include immuno-activation as well as immuno-inhibition and the specification lacks written description for immuno-activation.

Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making solvates of the claimed invention. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

1. **The nature of the invention:**

The invention is drawn to the compounds of formula (I), or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof. The specification is not adequately enabled to show how to make solvates of the compounds of formula (I). Unlike most applications which Examiner examines, this application does not give an explicit definition of "solvate." The compounds of formula (I) embrace heterocyclic compounds substituted with variable groups R, $R^1$, $R^3$, $R^4$, $R^6$, $R^7$, $R^8$, $R^9$, $R^{10}$, Alk, m, n, Q and X.

Even a cursory calculation of the number of compounds embraced in the instant formula (I) would result in at least hundreds of thousands of compounds. This is of course far more compounds than the specification enables one skilled in the art to make. Thus, the genus embraced in claim 1 is too large and there is no teaching of any solvate of this large genus.

2. **The state of the prior art:**

A search in the pertinent art, including water as solvent resulted in a pertinent reference, is indicative of the unpredictability of solvate formation in general. The state of the art is that it is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of an organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph of West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley, New York, 1988, 358. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph: "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". West, Anthony R., *Solid State Chemistry and Its Applications*, Wiley, New York, 1988, 365. Thus, in the absence of undue experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent is added per molecule of host.

3. **The predictability or lack thereof in the art:**

For the reasons stated *supra*, the solvates as applied to the above-mentioned compounds claimed by the Applicant are not art-recognized compounds and hence there should be an enabling disclosure in the specification with working example(s).

4. **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to solvates. There is no example of solvates of the instant compounds. A multiplicity of compounds were shown in the examples of the specification each of which come in contact with a solvent but there is no showing that the instant compounds formed solvates. Hence it is

clear that merely bringing the compounds in contact with solvent does not result in solvate and additional direction or guidance is needed on how to make them. The specification has no such direction or guidance.

5. **The presence or absence of working examples:**

There is no working example of any solvate formed. These cannot be simply willed into existence. "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." *Morton Int'l Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 28 USPQ2d 1190 (1993). The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be a showing of supporting evidence that solvates of these compounds exist and therefore can be made.

6. **The breadth of the claims:**

The breadth of the claims include all of the hundreds of thousands of compounds of formula (I) of claim 1 as well as the presently unknown list of potential solvate derivatives embraced by the word "solvate." The term is important in claim 1 because claims are to be given their broadest reasonable interpretation that is consistent with the specification. Because the specification does not adequately teach one skilled in the chemical arts how to sufficiently make the claimed solvates of the present invention without undue experimentation, the scope of the claims is broader than the scope of the specification. It would not be obvious to one skilled in the art how to make the solvates of the present invention. Therefore, the scope of enablement

provided to one skilled in the art by the disclosure is not commensurate with the scope of protection sought by the claims.

**7. The quantity of experimentation needed**

The specification has no support, as noted *supra*, for the desired solvates of the compound of formula (I). As noted above, the genus embraces hundreds of thousands of compounds and hence the breadth of the claims is broad. The quantity of experimentation needed would be an undue burden on one skilled in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated *supra*. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvates of the compound of formula (I) embraced in the instant claims.

In view of the seven factors, *supra*, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claims 27-29 are rejected under 35 U.S.C. 112, first paragraph, the specification does not reasonably provide enablement for immunomodulation or immuno-inhibition in mammals, including humans where the immunomodulation treats autoimmune disease, rheumatoid arthritis, multiple sclerosis, diabetes, asthma, transplantation, systemic lupus erythematosis and psoriasis. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the

amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

**1. The nature of the invention:**

As stated above, this invention relates to the compounds of formula (I), or a pharmaceutically or veterinarily acceptable salt, hydrate or solvate thereof. The compounds of formula (I) embrace heterocyclic compounds substituted with variable groups R, $R^1$, $R^3$, $R^4$, $R^6$, $R^7$, $R^8$, $R^9$, $R^{10}$, Alk, m, n, Q and X.

**2. The state of the prior art:**

A careful search to determine the state of the prior art at the time the invention was made reveals that although review articles were published showing the significance of the CD28/B7 costimulatory pathway being essential for the development and homeostasis of regulatory T cells that control spontaneous autoimmune disease, these review articles do not discuss a class of compounds, including instant compounds, which can effectively carry out this physiological mechanism. For instance, experimentally induced *models* of autoimmunity have been shown to be prevented or reduced in intensity in mice rendered deficient for CD28 costimulation. (Emphasis added). Salomon, Benoit, et al., *B7/CD28 Costimulation Is Essential for the Homeostasis of the CD4+CD25+ Immunoregulatory T Cells that Control Autoimmune Diabetes*, Immunity, Vol. 12, 431-440, April, 2000. It is clear that this reference shows that the state of the art at the time of the present invention dealt only with experimental models and not with the real world application of a class of compounds, including instant compounds, which effectively treat

autoimmune disease, rheumatoid arthritis, multiple sclerosis, diabetes, asthma, transplantation, systemic lupus erythematosis and psoriasis.

**3. The predictability in the art:**

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would recognize that with regards to the therapeutic effects, it would take undue experimentation to determine whether or not the compounds of formula (I) would be useful for treating autoimmune disease, rheumatoid arthritis, multiple sclerosis, diabetes, asthma, transplantation, systemic lupus erythematosis and psoriasis in a subject.

**4. Amount of guidance/working examples:**

The preparation of example compounds has been described on pages 32-66. The ability of the example compounds to demonstrate inhibitory effects on the CD80-CD28 interaction or on the production of IL-2 is shown on these same pages. While it seems that the assays done for this invention purport to show that the compounds of formula (I) tend to inhibit the CD80-CD28 interaction or the inhibition of the production of IL-2, it does not appear as though any experiments were conducted which definitely show that administration to a human patient would result in the treatment of autoimmune disease, rheumatoid arthritis, multiple sclerosis, diabetes, asthma, transplantation, systemic lupus erythematosis and psoriasis.

**5. The breadth of the claims:**

The breadth of claims is drawn to compounds, compositions and methods of immunomodulation or immuno-inhibition in mammals, including humans where the immunomodulation treats autoimmune disease, rheumatoid arthritis, multiple sclerosis, diabetes, asthma, transplantation, systemic lupus erythematosis and psoriasis.

6. **The quantity of undue experimentation needed:**

The quantity of experimentation needed would be an undue burden on one skilled in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated *supra*.

7. **The level of the skill in the art:**

The level of skill in the chemical arts is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

In view of the seven factors, *supra*, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

## *Duplicate Claims*

Claim 25 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim

to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The preamble does not give patentable weight to the claim.

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leeser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) toll-free at 866-217-9197. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

EL

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